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Title: Executive dysfunction predicts social cognition impairment in amyotrophic lateral sclerosis

Tamlyn J Watermeyer. Bangor University, Department of Psychology, Bangor, UK

Richard G Brown. King's College London, Institute of Psychiatry, Psychology & Neuroscience, London, Department of Psychology, UK

Katie C L Sidle. University College London, Institute of Neurology, Department of Molecular Neuroscience, London, UK

David J Oliver. Medway Community Healthcare Trust, The Wisdom Hospice, Kent, UK & University of Kent, The Centre for Professional Practice, Chatham, Kent, UK

Christopher Allen. Cambridge University Hospitals NHS Trust, Addenbrooke's Motor Neuron Disease Care & Research Centre, Cambridge, UK

Joanna Karlsson. East Kent Hospitals University NHS Trust, East Kent Motor Neurone Disease Service, Kent, UK

Catherine M Ellis. King's College Hospital NHS Foundation Trust, Motor Nerve Clinic, Academic Neurosciences Centre, London, UK

Christopher E Shaw. King's College London, Institute of Psychiatry, Psychology & Neuroscience, London, Department of Clinical Neuroscience, UK

Ammar Al-Chalabi. King's College London, Institute of Psychiatry, Psychology & Neuroscience, London, Department of Clinical Neuroscience, UK

Laura H Goldstein. King's College London, Institute of Psychiatry, Psychology & Neuroscience, London, Department of Psychology, UK

Corresponding author: Prof. Laura H Goldstein, P077 Department of Psychology, Institute of Psychiatry, Psychology & Neuroscience, King's College London, De Crespigny Park London SE5 8AF United Kingdom

Tel: +44207 848 0218 Fax: +440207 848 5006 laura.goldstein@kcl.ac.uk

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Abstract

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder of the motor system with recognised extra-motor and cognitive involvement. This cross-sectional study examined ALS patients' performance on measures requiring social inference, and determined the relationship between such changes and variations in mood, behaviour, personality, empathy and executive function. Fifty-five ALS patients and 49 healthy controls were compared on tasks measuring social cognition and executive function. ALS patients also completed measures examining mood, behaviour and personality. Regression analyses explored the contribution of executive function, mood, behaviour and personality to social cognition scores within the ALS sample. A between-group MANOVA revealed that, the ALS group was impaired relative to controls on two composite scores for social cognition and executive function. Patients also performed worse on individual tests of executive function measuring cognitive flexibility, response inhibition and concept formation, and on individual aspects of social cognition assessing the attribution of emotional and mental states. Regression analyses indicated that ALS-related executive dysfunction was the main predictor of social cognition performance, above and beyond demographic variables, behaviour, mood and personality. On at least some aspects of social cognition, impaired performance in ALS appears to be secondary to executive dysfunction. The profile of cognitive impairment in ALS supports a cognitive continuum between ALS and frontotemporal dementia.

Introduction

Amyotrophic lateral sclerosis (ALS) is the most prevalent form of motor neuron disease (MND). Approximately 10 - 15% of ALS patients fulfil criteria for frontotemporal dementia (FTD). However, non-demented ALS patients may show milder cognitive and behavioural symptoms [1, 2], indicating a possible cognitive continuum between ALS and FTD that might correspond to cerebral abnormalities common to both disorders [3]. ALS cognitive impairment is characterized by executive dysfunction [4], with growing evidence for language involvement [5]. Behavioural changes, including increased apathy and disinhibition have been noted [6], while modest evidence for ALS-specific personality traits exists [7]. Recently there has been interest in potential impairments in social cognition in ALS. Social cognition refers to cognitive processes that subserve the encoding and decoding of socially salient information, such as the emotions and intentions of others [8]. Converging evidence suggests that these processes are supported by a frontostriatal network [9], the disruption of which may underlie behaviour and personality changes associated with several neurodegenerative conditions [10]. The investigation of social cognition in ALS has focussed on basic emotion recognition and Theory of Mind (ToM), the ability to infer others' mental and emotional states so as to understand and predict their behaviour [11]. Deficits in the recognition of emotion from faces have been reported in ALS patients [2, 12, 13], albeit not consistently [14, 15], with one study suggesting that such impairments only emerge with FTD-comorbidity [16]. These studies have used a range of different measures and impairment criteria, across typically small samples ($n < 35$), sometimes including patients with FTD [12], all of which may contribute to the variance in findings reported. The investigation of ToM in ALS has relied exclusively on cartoons and written or video vignettes [see [17] for review]. Relative to healthy controls, people with ALS have shown difficulty with describing the intentions and feelings of characters [15, 18, 19], identifying and explaining social faux pas [20] and estimating characters' preferences for objects based on their eye gaze direction [13, 21].

Whether the reported deficits in social cognition are related to wider cognitive-behavioural impairment is unclear. Moderate correlations between behavioural scores and social cognition tasks have been found in some studies [13, 21]; but in general, behaviour is not commonly assessed alongside these measures. More frequently, social cognition performance has been associated with executive function indices [18, 20, 22], suggesting that executive dysfunction may partially underlie the observed impairments. Nonetheless, the respective contributions of behaviour, personality and executive function to ALS social cognition impairment remain unclear. We therefore sought to investigate the profile and extent of social cognition changes in the largest sample reported to date of patients with ALS without FTD, using an extensive battery of executive function and social cognition tasks. We also explored the relationship between social cognition in ALS and variations in executive function, everyday frontally-mediated behaviour, mood and personality.

The hypotheses for the study were as follows: (i) relative to controls, patients with non-demented ALS will show poorer performance on separate composites and individual tests of executive function and social cognition and (ii) executive function will be the main predictor of performance on a composite of social cognition, with smaller contributions from behaviour, mood and personality (above and beyond patients' age and years of education).

Methods

Participants

Fifty-five ALS patients, meeting criteria for definite, clinically definite, probable or laboratory-supported probable ALS [23], without co-morbid FTD were recruited from MND Care and Research Centres across London, Cambridge and Kent in the UK. Forty-nine age-, gender- and education-matched healthy control (HC) participants were recruited through a volunteer database. Participants were recruited between January 2011 and May 2013. Exclusion criteria for all participants were: a diagnosis of another neurological or a psychiatric condition or diabetes; aged > 75 years; a first language other than English; a clinical diagnosis of dementia and respiratory insufficiency, as determined by the patients' clinical team, a forced vital capacity < 70% (where available) and a score > 10 on the Epworth Sleepiness Scale [24].

Cognitive and behavioural measures

Premorbid and current IQ were estimated using the Wechsler Test of Adult Reading [25] and the Wechsler Abbreviated Scale of Intelligence [26], respectively. The modified Hospital Anxiety and Depression Scale (HADS) [27] measured symptoms of anxiety and depression. In the patients, functional abilities were assessed using the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) [28].

Social cognition was assessed using a variety of measures used in previous studies of ALS but not together [13, 15, 18]: the Reading the Mind in the Eyes task (RME) [29]; three subtests of The Awareness of Social Inference Test (TASIT) [30] and three subtests of the Happé Cartoon and Written Scenarios tasks [31]. Executive function was assessed using the sorting and description trials of the Card Sorting Task of the Delis-Kaplan Executive Function Test (D-KEFS) [32]; the 'S' and 'C' trials of the modified Verbal Fluency Index (VFI) [33] and number of errors on the Brixton Test [34]. Testing also included one language and one memory test (see Tables S1 and S2, Online Resource 1). Measures used to assess behaviour, empathy, emotional lability and personality were: the Frontal Systems Behaviour Scale (FrSBe) [35]; the Interpersonal Reactivity Index (IRI) [36]; the ALS-specific Emotional Lability Questionnaire (ELQ) [37] and the NEO-Five-Factor-Inventory (NEOFFI) [38], respectively. Details of the specific components measured for each test are

provided in Table 1. All tests and measures were untimed except for the VFI which contains a control condition to account for writing speed. For the D-KEFS sorting task, administration was discontinued when the participant had completed 10 attempted sorts, attained all the target sorts or indicated that he or she could not generate any sorts after a prompt.

Statistical analysis

To reduce the likelihood of making Type 1 errors through multiple comparisons of individual test scores, composites for executive function and social cognition were created. Test scores for individual ALS patients were first standardised on the control group by subtracting the control group mean score from each patient's score on that test and dividing the difference by the corresponding control group standard deviation (SD). Where necessary, scores were reflected so that higher scores all indicated worse performance. The standardised scores within each domain were then summed and divided by the number of component measures to give and Executive composite and Social Cognition composite. Where there were missing data (see Table 3), the composite was divided by the number of tests completed. Composite scores showed satisfactory internal consistency (Executive: $\alpha = 0.78$; Social Cognition: $\alpha = 0.83$). Between-group comparisons were undertaken using t-tests or multivariate analysis of variance (MANOVA). Pearson's correlations and multiple regression (MR) analyses were used to examine the relationships between variables. Outliers were identified using the Median Absolute Deviation Method [39] and transformed to reduce their impact on analyses. Univariate normality was assessed using the D'Agostino–Pearson Omnibus Test [40], while multivariate normality was assessed using the Shapiro-Wilks Multivariate test [41], available in R Version 3.0.1 [42]. Non-normal distributions, including the composite scores, were transformed using Naperian log transformation. Statistical significance was set at $p < 0.05$. Between-group differences were also presented in terms of effect sizes: either Cohen's d, partial eta squared ($\eta\rho^2$) and Cramer's V. Between-group comparisons, percentile and regression analyses were performed using IBM SPSS Version 21.0 [43].

Results

Demographic and clinical characteristics

The ALS and HC groups comprised 15 (27.4%) and 15 (30.6%) females, respectively. There was no difference between the ALS and HC groups with respect to gender [$\chi^2(1) = 0.14$, $p = 0.71$, Cramer's V = 0.04]; age [$t(102) = -0.14$, $p = 0.89$, d = 0.03]; years of education [$t(100.13) = -0.002$, $p = 0.10$, d = 0.00]; current IQ [$z = -1.06$, $p = 0.29$, r = -0.10] or estimated premorbid IQ [$z = -0.95$, $p = 0.34$, r = -0.14]; the HADS Total score [$z = -0.69$, $p = 0.49$, r = -0.07] or the depression [$z = -1.58$, $p = 0.12$, r = -0.15] or anxiety [$z = -0.27$, $p = 0.79$, r = -0.03] subscales (Table 2). The mean patient

ALSFRS-R score at the time of assessment was 34.05 (SD 7.80). Approximately 76% of the patients had limb-onset and approximately 24% had bulbar-onset disease. The average time since onset of symptoms was 31.8 months (SD 18.5), with a median delay from symptom onset to diagnosis of 12.0 months (IQR 8.0-21.0).

Cognitive function and behaviour

Figure 1 shows the mean composite scores for the patient and control groups. A one-way MANOVA revealed an overall group difference [$F(2,101) = 4.68$, $p = 0.01$, Wilks' Lambda = 0.92, $\eta\rho^2 = 0.09$], with univariate contrasts revealing that the patients were more impaired on both the Executive composite [$F(1,102) = 8.6$, $p = 0.004$, $\eta\rho^2 = 0.08$] and the Social Cognition composite [$F(1,102) = 5.53$, $p = 0.02$, $\eta\rho^2 = 0.05$].

To aid interpretation of these overall effects, performance on individual executive and social cognition tests was explored using two-tailed t-tests (Table 3). Patients performed less well than HCs on the D-KEFS sorting errors [$t(100) = -2.7$, $p = 0.009$, d = 0.55]; D-KEFS description errors [$t(100) = -3.2$, $p = 0.002$, d = 0.63] and the VFI 'C' trial [$t(86.9) = -2.2$, $p = 0.03$, d = 0.35]. A trend was found for the VFI 'S' trial [$t(93.5) = -1.8$, $p = 0.08$, d = 0.42]. No group difference was found for Brixton errors. For social cognition, patients performed worse than HCs on the Happé Cartoon Single Inference test (C-Sin) [$t(91) = -4.87$, $p < 0.001$, d = 1.01], Happé Cartoon Pairs Inference test errors (C-Pairs) [$t(91) = -3.2$, $p = 0.002$, d = 0.67] and the Happé Written Scenarios test (Scenarios) [$t(81) = -2.82$, $p = 0.006$, d = 0.62]. No differences were found for any of the TASIT subtest scores or the RME errors score. Figure 2 shows the standardised scores of the ALS group (scores all zero for the HCs) for the different tasks. Table 3 displays the proportion of ALS patients performing at or below the 5th percentile of the control group on the composites and cognitive tasks. Table 3 also displays the proportion of patients meeting criteria for clinically relevant behaviour (FrSBe), 'extremely high' or 'extremely low' levels of personality traits (NEOF-FFI) and whose self-ratings were at or below the 5th percentile of the control group for empathy (IRI) and emotional lability (ELQ).

The number of patients meeting current criteria for cognitive impairment [44], impairments on two or more tests of executive function, was 4/55 (7.3 %). The number of patients meeting criteria for behavioural impairment, defined here as showing clinically relevant behaviour on two or more domains of the FrSBe, was 15/51 (29.4 %). By extension, and for exploratory purposes, the number of patients showing two or more impairments on the social cognition tasks and thereby meeting criteria for social cognition impairment was 6/55 (10.9 %). The individual cognitive and behavioural profiles of these six patients are displayed in Table 4. Two of the six patients also qualified for cognitive impairment (≥2+ impairments on executive function tasks). One of the six patients qualified for behavioural impairment (≥2+

impairments on FrSBe). That same patient reported that their level of empathic concern was lower than the 5th percentiles of the control group.

Predictors of social cognition in ALS patients

Predictors of social cognition function within the ALS group were investigated using Executive and Social Cognition composite scores restandardised using the ALS group's means and SDs so as to investigate the relationship between social cognition and executive function within the ALS sample [Executive: $\alpha = 0.80$; Social Cognition: $\alpha = 0.88$]. This approach has been used in other ALS studies [5]. Possible predictors (demographic, disease, mood, personality, behaviour and Executive function scores) were chosen on the basis of previous findings from ALS studies [2, 4-7, 12-16, 18-22] and statistical criteria, such as a linear relationship with the Social Cognition composite. Mean scores for the subscales of the FrSBe, NEOFFI and IRI, relevant to these analyses, are reported for reference in Table 3.

Bivariate correlational analyses were first conducted to identify significant relationships between potential predictor variables and the Social Cognition composite ($p < 0.05$, see Table S3, Online Resource 1). Significant associations with the Social Cognition composite were found for: the Executive function composite [r = 0.61, p <0.001]; FrSBe Total [r = 0.35, p = 0.01]; HADS Total [r = -0.27, p = 0.05]; NEOFFI Openness T-score [r = - 0.32, p = 0.01]; age in years [r = 0.44, p = 0.001] and years of formal education [r = -0.29, p =0.03]. These variables were entered into a multiple regression with the Social Cognition composite as the dependent variable. To better assess the contribution of executive functioning, the independent variables were entered in a hierarchical design in the following stages: Stage 1: Age and education (control variables); Stage 2: FrSBe Total, HADS Total and NEOFFI Openness T-score; Stage 3: Executive Function Composite (See Table S4, Online Resource 1). The final model, with all predictor variables entered into the equation, predicted 44.5% of the variance in the Social Cognition composite. In the final model the executive function composite was the only predictor [standardised $\beta = 0.49$, 95% CI (0.24; 0.72), $t(46) = 3.98$, $p < 0.001$].

Discussion

This study used an extensive battery of social cognition measures, alongside standardised measures of executive function, behaviour and personality in a relatively large sample of people with ALS without dementia. Even though as a group there was evidence of only mild executive dysfunction on formal tests, the results suggest a strong association between executive function and social cognition, with 45% shared variance on the ALS group composite scores. As a group, those with ALS performed worse than controls matched for age, education, gender and IQ on a composite measure of social cognition, with impairment on individual tasks that required the attribution of complex thoughts,

feelings and beliefs to characters in cartoons and social stories (Happé tasks). In contrast, other aspects of social cognition were intact. The patient group was unimpaired on a measure of empathy, the ability to identify emotion in the faces of others, or to identify and interpret sarcastic exchanges between actors simulating everyday social interaction on the TASIT. The finding that group effects were elicited on the Happé task and not the TASIT social inference subtasks might be due to the greater complexity of the former measure. While both tasks seemingly require similar processes, the TASIT places less demands on the integration of abstract information and no effortful expression of this integration into a coherent narrative (the TASIT requires only a forced-choice response). The TASIT thus places fewer demands on executive function, a mechanism suggested to underlie previously reported deficits on the Happé tasks in ALS and FTD [18, 45]. The current study failed to replicate the ALS group deficits reported previously on the TASIT [15]. At the individual level, some participants with ALS showed difficulty with the sarcastic exchanges, particularly on the SI-M component of the task where additional contextual cues, such as a visual cue or a scene prologue, were not available to aid interpretation (see Table 3). These results underscore the heterogeneity of performance within ALS samples on social cognition measures and the importance of replicating findings with adequate representative samples. Previous reports of emotion identification deficits in ALS have been variable [17]. In the current sample, impairments on the RME and the emotion recognition condition of the TASIT were noted when individual patient performance was compared with the control group (Table 3). These deficits might reflect a more severe manifestation of social cognitive impairment; possibly a harbinger for the progression of ALS-FTD [16].

Cerebral atrophy in ALS may extend beyond the motor cortices to the prefrontal and temporal regions, areas implicated in FTD [3]. In the behavioural variant of FTD (bvFTD), overt behavioural and personality changes represent hallmarks of the disease [46] and may reflect a breakdown in higher order social cognitive processes, such as emotion attribution and the understanding of social situations. Such change in turn may correspond to cortical atrophy along a frontotemporal gradient [47]. The finding of an overall impairment on the Social Cognition composite in the current ALS sample, as with previous reports, therefore reinforces the notion of a cognitive overlap between ALS and FTD, possibly implicating common neuropathology. For example, impairment on the Happé social situation tasks, which require the inference of intentions, beliefs and emotions from characters in cartoons or social stories is found in ALS (here and [18]) and in FTD [45], although as noted above, this may reflect executive impairment rather than an underlying deficit in social cognition. Some differences, however, are apparent. As noted above, unlike in FTD [48], the ALS group in the present study did not show impaired recognition of facial emotion. Neither did they show difficulty in identifying sarcastic exchanges between actors simulating everyday social interaction on the TASIT. Such social cognition impairments may require the more developed pathology seen in FTD, and be less characteristic of pure ALS.

Although the results of the regression analysis indicated a significant association between executive function and social cognition, there was no evidence of a significant independent contribution of mood, personality or other behavioural features of ALS. Further, of the six patients who were impaired on two or more tests of social cognition, only one met criteria for behavioural impairment and reported reduced empathy relative to controls. While this may indicate that such factors are unrelated to social cognition, the result should not necessarily be generalised to patients with ALS showing more marked mood, personality or behavioural change. Moreover, the current study used patients' self-ratings to measure these domains and thus the possibility of reduced insight into their own neuropsychiatric change cannot be excluded. This caveat potentially limits the inferences drawn regarding the contribution of patients' neuropsychiatric symptoms to their performance on the social cognition tasks. The only personality domain to correlate significantly with the Social Cognition composite was the NEO-FFI Openness T-score, with less Openness associated with worse social cognition. People who score low on this trait typically feel emotion less intensely than others and are less attentive to forms of experience, such as fantasy and intellectual curiosity [49]. The presence of this relationship is therefore meaningful.

Executive functioning alone was sufficient to predict a significant proportion of the variability in the Social Cognition composite; however, a notable proportion (55%) remained unexplained. Future research is required to identify additional sources of variance, although some error variance will always be present. For example, aspects of higher level language functioning may contribute to variability in social cognition in ALS. Performance on social cognition measures and the non-literal aspects of language have been indicated in neurological patients [50]. In turn, the processing of non-literal speech has been correlated with executive function and semantic knowledge in bvFTD patients [51] and syntactic competence in aphasic FTD patients [52]. There is increasing recognition of language involvement in ALS, including semantic processing and syntactic comprehension, in non-demented patients with ALS [5, 53], which may co-occur or be independent of executive function [5]. Future research should investigate whether a complex relationship between executive function, language processing and social cognition can explain performance on social cognition measures by people with ALS.

The clinical relevance of the cognitive deficits shown by the current ALS sample deserves consideration. Patients exhibiting executive deficits may potentially have difficulties managing financial affairs, planning for future events or arriving at decisions regarding their clinical care. Early screening for cognitive impairment in ALS, would aid the direction of care strategies. While overall the ALS patients showed no difficulty with emotion recognition, they did show difficulty interpreting the intentions and beliefs of cartoon and story characters. This highlights the possibility that people

with ALS may respond appropriately to other people's emotions, but be less able to anticipate or infer the thoughts or intentions of those around them. This can place strain on the patient's interpersonal relationships which become more important as their dependency on others increases with their functional decline. The implications for and education of the caregiver with regards to possible interpersonal changes in the patient should be considered in clinical consultations with ALS families. Clinic screening assessments may, therefore, also usefully include aspects of social cognition [53].

This study is not without limitations. The focus of the assessment was on social cognition and executive function, with only a brief assessment of memory and basic aspects of language function (see Tables S1 and S2, Online Resource 1). The use of composite scores, while necessary to avoid the possibility of increased family-wise error rate, may have masked associations for individual measures. Likewise, the z-score method used for creating the composite scores assumes that each task is equally difficult and that each component carries equal weighting in the overall score, which may not be the case. As mentioned, the reliance on patients' self-ratings without proxy-ratings of empathy, behaviour and personality may have underestimated the nature and severity of neuropsychiatric changes in the sample. The lack of objective measures to determine respiratory insufficiency in patients leaves open the possibility that some of the cognitive deficits reported here may have been influenced by the inclusion of patients who themselves or their clinician were unaware of subtle decrements in respiratory functioning. Nonetheless, the current study revealed a profile of FTD-like cognitive impairments, in the domains of executive function and some aspects of social cognition, in a large sample of non-demented ALS patients. It also further qualified the relationship between social cognition and executive dysfunction in ALS, indicating that impaired performance on at least some social cognition tasks in people with ALS may be attributable primarily to the executive components of those tasks. More research is needed to substantiate this claim. It is possible that more marked impairments in social cognition, less linked to executive processes, may not emerge until pathological FTD-like progression. Longitudinal study with evidence for the progression of FTD-like social cognition impairments in ALS patients would provide further support for a cognitive continuum between ALS and FTD.

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical Standards

Ethics approval was obtained from the National Research Ethics South East London Research Ethics Committee 4 (11/H0807/1). Informed written consent was obtained from all participants. Ethical standards were consistent with the 1964 Declaration of Helsinki and its later amendments.

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Table 1 Descriptions of tasks and questionnaires

Task or Questionnaire	Description
Reading the Mind in the Eyes (RME) [29]	Participants are presented with images of faces showing only the eye region. They must select one out of four words (e.g. 'playful', 'serious', 'reflective', 'impatient') which they believe best describes the mental or emotional state of the presented face.
The Awareness of Social Inference Test (TASIT) [30]	Participants are presented with enacted vignettes of everyday social interactions. In the Emotion Recognition (ER) condition, actors enact ambiguous dialogue using dynamic emotion expression (Happy, Surprised, Sad, Angry, Anxious, Revolted, Neutral). Participants must identify the emotions of the actors. In the Social Inference–Minimal (SI-M) and Social Inference-Enriched (SI-E) conditions, actors portray everyday conversational exchanges making use of paralinguistic information to reveal or conceal their intentions and feelings (e.g. sarcasm, white lies). The SI-E condition provides additional contextual cues to indicate the true state of affairs (e.g. a visual cue or a prologue to the scene). In both conditions, participants must respond to closed-ended questions (requiring 'yes', 'no' or 'don't know' responses) regarding what actors are thinking, feeling, doing and explicitly or implicitly saying.
Happé Cartoon and Scenarios [31]	Participants are presented with humorous cartoons and vignettes depicting social situations involving deception, belief, intention and feelings. Participants must describe what is humorous about the cartoons and how or what the characters in the vignettes are feeling and thinking. In the first cartoon condition, participants are presented with single cartoons, while in the second forced-choice condition they are presented with two cartoons and asked to choose which of the two is humorous and explain why.
Card Sorting	From the Delis-Kaplan Executive Function Scale (D-KEFS) [32]. In the Card Sorting condition, participants categorize cards into sorts on the basis of information displayed on the cards. This information can be verbal (e.g. words belonging to a category, such as animals) or visual (e.g. cards of similar size or shape). In the Description condition, participants describe the relationships between cards within each created category.
Verbal fluency index (VFI) [33]	Participants write down/say as many words as they can beginning with S and four-letter words beginning with C in five and four minutes respectively. In subsequent

	motor control conditions, the participant is timed as they copy/read out these words as quickly as they can. Higher scores indicate longer thinking times and worse performance.
The Brixton Spatial Anticipation Test [34]	Participants are presented with a booklet of pages showing a sequence of stimuli (circles). Each page contains one coloured circle. As the examiner turns the page, the position of the coloured circle changes. Participants must determine the position of the next coloured circle in an array based on the positions of previous coloured circles.
The Frontal Systems Behaviour Scale (FrSBe)[35]	46 items measure current everyday behavioural aspects of executive function. Participants rate the frequency with which they display certain behaviours on a scale of 1 (almost never) to 5 (almost always). Total and subscale T-scores (Apathy, Disinhibition, and Executive Dysfunction) are computed using normative data. A T-score > 65 indicates clinically relevant symptomatology.
The Interpersonal Reactivity Index (IRI) [36]	14 items measure empathic behaviour, such as a tendency to assume others' psychological perspective (perspective-taking) and sympathetic feelings towards others (empathic concern). Participants endorse whether an item describes them well on a scale of 1 (Does not describe me well) to 5 (Describes me very well). Higher scores indicate greater levels of empathy.
The Emotional Lability Questionnaire (ELQ) [37]	33 items measure the frequency and severity of incongruous episodes of laughing, crying, and smiling. Participants rate how often they experience these episodes on a scale of 0 (Never) to 3 (Frequently). Where relevant, participants also endorse the nature of these episodes on 4-point Likert scales, where higher scores indicate greater levels of perceived emotional lability.
The NEO Personality Inventory (NEOFFI) [38]	60 items measure five domains of personality (Neuroticism; Extraversion; Openness; Agreeableness; Conscientiousness). Participants endorse statements along a 5-point scale, ranging from 'Strongly Disagree' to 'Strongly Agree'. T-scores are derived using normative data.

Table 2 Demographic, IQ and mood measures

Demographics	**Mean (SD)**			
	ALS	**Controls**		
Age (years)	60.3 (8.5)	60.0 (9.7)		
Education (years)	14.5 (3.5)	14.5 (2.7)		
	Median (IQR)			
	ALS	**Controls**		
IQ Measures				
Predicted premorbid FSIQ	112.0 (108.0-116.0)	114.0 (107.0-117.5)		
WASI FSIQ	117.0 (109.0-122.8)	119.0 (112.5-125.0)		
Mood			**Cases N (%)**	
			ALS	**Controls**
HADS Anxiety	4.0 (2.0-6.0)	3.0 (2.0-6.0)	9 (16.4)	6 (12.2)
HADS Depression	2.0 (1.0-4.0)	1.0 (0.0-3.5)	3 (5.5)	0 (0)
HADS Total	6.0 (4.0-10.0)	6.0 (3.0-9.0)	2 (3.6)	0 (0)

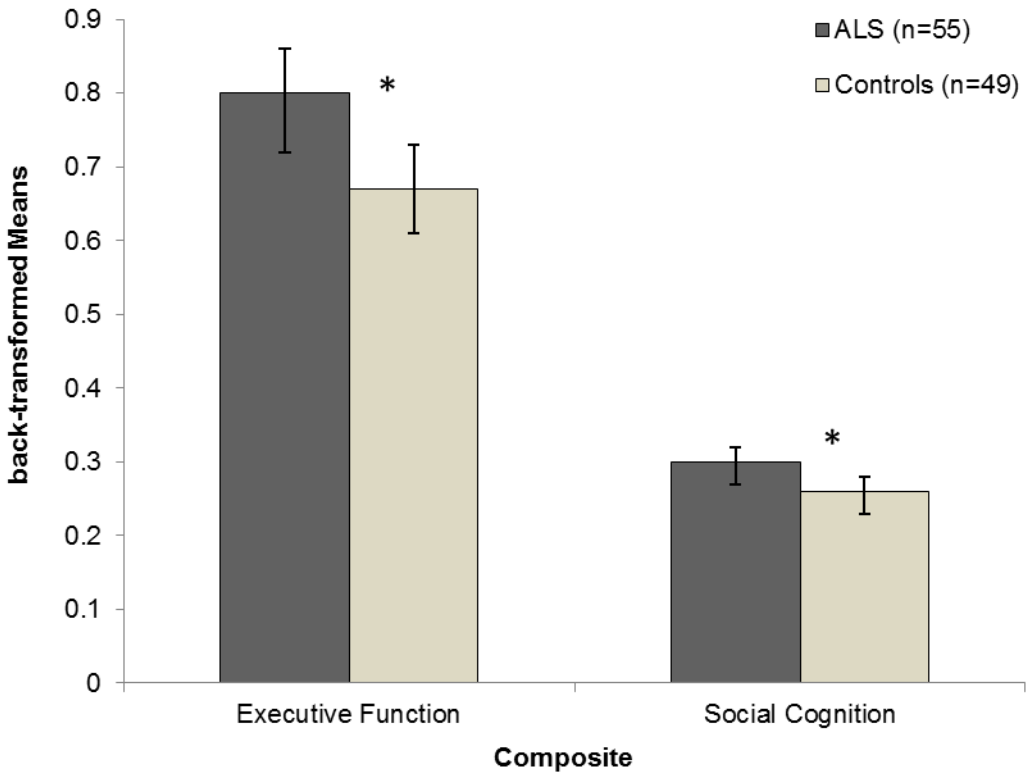
WASI, Wechsler Abbreviated Scale of Intelligence; FSIQ, Full Scale IQ; HADS, Hospital Anxiety and Depression Scale (modified; higher scores indicate worse mood). ALS N=55, Controls N=49 for all measures except predicted pre-morbid FSIQ ALS N=51, Controls N=49; WASI FSIQ, ALS N=48, Controls N=49. Higher HADS scores indicate greater levels of depression or anxiety; 'caseness' determined as per revised criteria [27].

Table 3 Performance and ratings on measures of executive function, social cognition, behaviour and personality

Measure (max possible)	**Mean (SD)**		**Cut-off**	**ALS No. (%)[a]**	**ALS N**
	ALS	**Controls**			
Executive function composite	0.5 (1)	0.0 (0.7)	1.6	7 (12.7)	55
VFI 'S' Trials	5.2 (3.3)	4.2 (2.1)	8.6	10 (18.2)	55
VFI 'C' Trials	16 (11.7)	12.1 (6.6)	20.7	3 (5.5)	55
DKEFS Card Sorting (32)	6.1 (2.1)	4.9 (2.3)	12.0	2 (3.8)	53
DKEFS Card Sorting Description (64)	26.6 (10.6)	20.5 (8.4)	47.0	3 (5.7)	53
Brixton Errors (55)	18.3 (5.8)	16.3 (6.4)	29.5	5 (9.1)	55
Social cognition composite	0.4 (0.8)	0.0 (0.7)	1.7	4 (7.3)	55
TASIT Emotion Recognition (28)	5.9 (2.5)	5.3 (2.7)	11.0	3 (5.5)	55
TASIT Social Inference-Minimal (60)	10.6 (6.7)	8.8 (5.6)	17.0	10 (18.2)	55
TASIT Social Inference-Enriched (64)	12.7 (6.6)	12.7 (6.1)	25.0	2 (3.6)	55
Happé Single Cartoon (32)	12.0 (5.2)	7.0 (4.7)	20.6	5 (11.1)	45
Happé Cartoon Pairs (30)	11.6 (4.6)	8.3 (5.1)	18.6	0 (0)	45
Happé Scenarios (30)	9.6 (4)	7.0 (4.2)	19.1	1 (2.6)	38
RME Errors (36)	10.5 (4.8)	9.9 (4)	17.0	7 (13)	54
Behaviour and Personality					
FrSBe Total score	60.1 (14.4)	59.9 (14.1)	65	15 (29.4)	51
FrSBe Apathy	61.1 (15.3)	55.6 (11.8)	65	17 (33.3)	51
FrSBe Executive Dysfunction	55.8 (12.7)	58.9 (13.3)	65	12 (23.5)	51
FrSBe Disinhibition	57.3 (12.4)	59.5 (15)	65	12 (23.5)	51
NEO-FFI Neuroticism	44.3 (8.9)	54.1 (9.2)	35/65	8 (15.4) / 0 (0)[c]	52
NEO-FFI Extraversion	50.8 (11.8)	49.0 (10.5)	35/65	0 (0) / 4 (7.7)[c]	52
NEO-FFI Openness	50.3 (9.6)	48.8 (12.3)	35/65	3 (5.8) / 4 (7.7)[c]	52
NEO-FFI Agreeableness	50.4 (11.5)	55.1 (10.6)	35/65	5 (9.6) / 3 (5.8)[c]	52
NEO-FFI Conscientiousness	47.3 (11.1)	44.8 (13.9)	35/65	4 (7.7) / 2 (3.8)[c]	52
IRI Perspective Taking (28)	17.0 (5.2)	18.2 (4.0)	10.0	4 (7.3)	55
IRI Empathic Concern (28)	19.3 (5.3)	19.2 (4.1)	12.0	6 (10.9)	55
ELQ Total Score (93)	7.0 (0.0-20.0)[d]	0.0 (0.0-5.0)[d]	21.0	13 (23.6)	55

Legend (Table 3)

Higher scores indicate worse performance or greater impairment except for IRI. [a]Number and percentage of patients with performance or ratings at or below 5th percentile of controls (composites, cognitive tests scores, IRI and ELQ); meeting cut-off criteria for clinically relevant behaviour (FrSBe) and 'extremely high' or 'extremely low' levels of personality trait (NEO-FFI). [b]Means derived from untransformed data. [c]35 = cut-off for 'extremely low', 65 = cut-off for 'extremely high'. [d]Median (IQR). VFI, Verbal Fluency Index; DKEFS, Delis-Kaplan Executive Function Scale; TASIT, The Awareness of Social Inference Test; RME, Reading the Mind in the Eyes; FrSBe, Frontal Systems Behaviour Scale; NEO-FFI, Neo-Five-Factory Inventory; IRI, Interpersonal Reactivity Index; ELQ, Emotional Lability Questionnaire. Control N=49 for all measures except: Happé Cartoons, N=48; Happé Scenarios, N=45; FrSBe, N=48; NEO-FFI, N=48.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ALS (n=55)
Controls (n=49)
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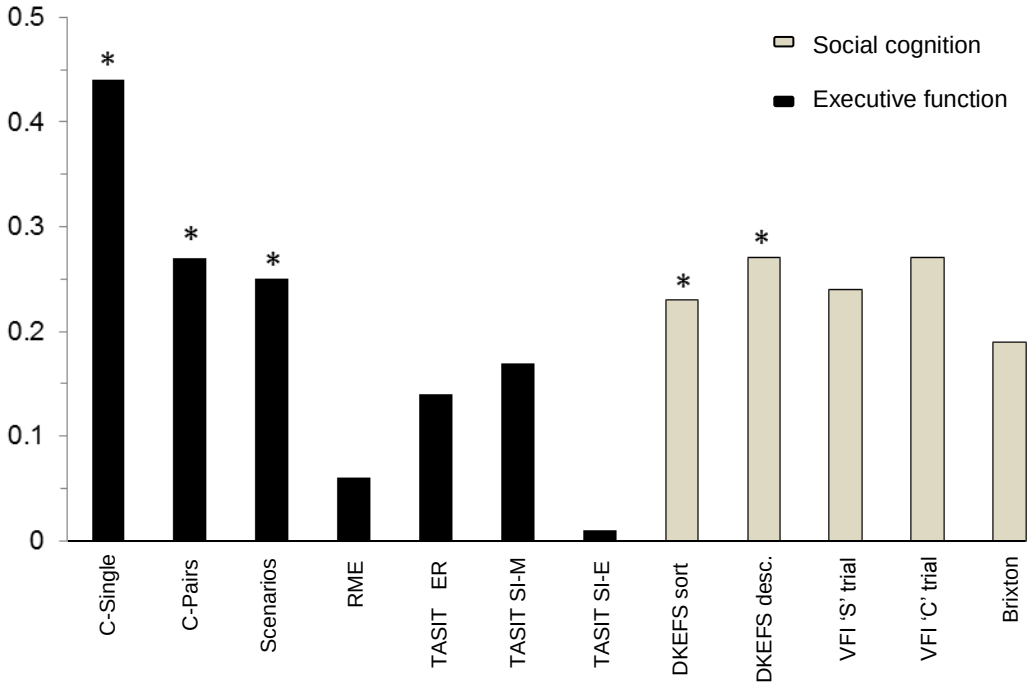
Executive Function
Social Cognition
Composite

Figure 1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C-Single
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Scenarios
RME
TASIT ER
TASIT SI-M
TASIT SI-E
DKEFS sort
DKEFS desc.
VFI 'S' trial
VFI 'C' trial
Brixton

Figure 2

Supplementary material.

Executive dysfunction predicts social cognition impairment in amyotrophic lateral sclerosis

Journal of Neurology

Tamlyn J Watermeyer , Richard G Brown, Katie C L Sidle, David J Oliver, Christopher Allen, Joanna Karlsson, Catherine M Ellis, Christopher E Shaw, Ammar Al-Chalabi, Laura H Goldstein (correspondence: laura.goldstein@kcl.ac.uk. Institute of Psychiatry, Psychology & Neuroscience, King's College London)

Table S1: Language: Graded Naming Test (GNT)[1]

Between-group comparison	**Median (IQR)**		X^2 (*df*)	*p*	φc	**95% CI**
	ALS (n=55)	**HC (n=49)**				
GNT (max 30)	23 (14-29)	24 (22-26)	0.6 (1)	.44	.08	-1.0; 2.0

p–values from Medians test. *Note*: Higher score indicates better performance for group–level analysis; φc, Cramer's V; 95% CI, confidence interval for difference between medians

Table S2: Memory: California Verbal Learning Test (CVLT)[2]

Between-group comparison	**Mean (SD)**		*t*(*df*)	*p*	*d*	**95% CI**
Standardized scores (min-5; max 5)	**ALS (n=51)**	**HC (n=49)**				
Immediate free recall **	50.1 (12.4)	53.6 (11.5)	1.3 (98)	.20	-0.29	-1.7; 8.6
Short delay free recall	0.1 (1.3)	0.1 (1.3)	2.5 (98)	.80	0.07	-0.4; 0.6
Long delay free recall	0.04 (1)	0.2 (0.9)	1.0 (98)	.31	-0.17	-0.2; 0.6
Long delay cued recall	-0.2 (1)	0.2 (1)	1.7 (98)	.09	-0.37	-0.1; 0.7

p–values from two–tailed t–tests.** T–score (min 5; max 95); *d*, Cohen's d; 95% CI, confidence interval for difference between means. *Note:* Higher score indicates better performance for recall trials.

1. McKenna, P., & Warrington, E. K. (1983). The Graded Naming Test. Cambridge, UK: Cambridge Cognition Limited

2. Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. (2000). California Verbal Learning Test: Second Edition. San Antonio, TX: Psychological Corporation.

Table S3. Correlations between potential predictor variables and Social Cognition composite

Potential predictors	***r (p)***
Demographic variables	
Age	**0.44 (.001)**
Education	**-0.29 (.03)**
Disease factors	
Symptom onset (bulbar/Spinal)	-0.17 (0.22)
ALSFRS-R Total score	0.07 (0.63)
ALSFRS-R Bulbar score*	-0.16 (0.25)
ALSFRS-R Limb score*	0.13 (0.33)
ALSFRS-R Respiratory score*	0.08 (0.55)
Disease progression rate**	-0.02 (0.88)
Mood	
HADS Anxiety	-0.26 (0.06)
HADS Depression	-0.24 (0.08)
HADS Total	**-0.27 (0.05)**
Behaviour	
FrSBe Total	**0.35 (0.01)**
ELQ Total	-0.07 (0.63)
NEOFFI Neuroticism	0.06 (0.66)
NEOFFI Extraversion	0.07 (0.62)
NEOFFI Openness	**-0.32 (0.01)**
NEOFFI Agreeableness	-0.07 (0.64)
NEOFFI Conscientiousness	0.18 (0.20)
IRI Perspective Taking	0.11 (0.41)
IRI Empathic concern	0.04 (0.77)
Cognition	
Executive function composite	**0.61 (<0.001)**

*ALSFRS–R: bulbar=items 1–3; Limb=items 4–9; respiratory=items 10–12. **Disease progression rate =(48-ALSFRS–R total) /months since symptom onset. ALSFRS-R, Amyotrophic Lateral Sclerosis Rating Scale-Revised; FrSBe, Frontal Systems Behavior Scale; HADS, Hospital Anxiety and Depression Scale (modified);NEOFFI, NEO-Personality Inventory**;** IRI, Interpersonal Reactivity Index

Table S4. Results of hierarchical regression model for Social Cognition composite scores

Step (Independent variable)	B	Standard Error B	Standardized B	95% CI for B
1. Constant	-1.14	0.72		-2.6; 0.3
Age	0.31	0.01	**0.39***	0.01; 0.1
Education (years)	-0.05	0.02	**-0.29**	-0.1; -0.01
2. Constant	-1.03	0.79		-2.6; 0.6
Age	0.02	0.01	**0.29**	0.001; 0.1
Education (years)	-0.03	0.03	-0.17	-0.1; 0.0
FrSBe Total	0.01	0.01	0.23	-0.0; 0.0
HADS Total	-0.03	0.02	-0.20	-0.1; 0.0
NEOFFI Openness	-0.01	0.01	-0.13	-0.0; 0.0
3. Constant	-0.52	0.69		-1.9; 0.9
Age	0.02	0.01	0.20	0.0; 0.0
Education (years)	-0.01	0.03	-0.06	-0.1; 0.4
FrSBe Total	0.01	0.01	0.10	-0.0; 0.0
HADS Total	-0.03	0.02	-0.24	-0.1; 0.0
NEOFFI Openness	-0.01	0.01	-0.11	-0.2; 0.0
Executive Function	0.48	0.12	**0.49***	0.2; 0.7

N=48. Results where $p< 0.05$ shown in **bold**. Results where $p<.001$ in **bold***. 1. $R^2=.240$, adjusted $R^2=.206$; 2. $R^2=.330$, adjusted $R^2=.250$; 3. $R^2=.516$, adjusted $R^2=.445$. FrSBe, Frontal Systems Behavior Scale; HADS, Hospital Anxiety and Depression Scale (modified); NEOFFI, NEO-Personality Inventory.

Table 4 Cognitive and behavioural profile of six patients showing two or more impairments on social cognition tasks

Patient	Total impairments on executive function tasks	Total impairments on social cognition tasks	HADS A score	HADS D score	IRI PT impaired	IRI EC impaired	Apathy impaired	Disinhibition impaired	Executive Dysfunction impaired	Very High NEO-FFI	Very Low NEO-FFI
001	1	2	1	3	No	No	Yes	No	No	A	N; E
002	1	2	1	0	No	Yes	Yes	Yes	No	E; C	No
003	4	5	0	0	No	No	No	No	No	A	N; O
004	2	2	3	1	No	No	Yes	No	No	Did not complete	
005	1	3	8	0	No	No	No	Yes	No	E	No
006	0	3	4	3	No	No	No	No	No	No	No

NEO-FFI: A, Agreeableness; E, Extraversion; O, Openness; C, Conscientiousness

Fig. 1 Mean composite scores. Higher scores indicate greater impairment

*p < 0.5, Error bars represent back transformed confidence intervals

Fig. 2 ALS group Z-scores for individual components of composites. Higher scores indicate greater impairment. C-Single, Happé Cartoon Single Inference; C-Pairs, Happé Cartoon Pairs; Scenarios, Happé Social Scenarios; RME, Reading the Mind in The Eyes Test; TASIT, The Awareness of Social Inference Test; ER, Emotion Recognition; SI-M, Social Inference-Minimal; SI-E, Social Inference-Enriched; DKEFS, Delis-Kaplan Executive Function System; desc., description; VFI, Verbal Fluency Index

*significantly different from the control group.